## REMARKS

In accordance with the forgoing, claim 1 has been amended, and claims 2, 4 to 5, and 7 to 45 have been canceled without prejudice or disclaimer of the subject matter contained therein. Upon entry of the amendment, claims 1, 3, and 6 are pending and under consideration.

A. Objections to the Specification

The disclosure is objected to due to an incomplete reference to a co-pending patent application. The current amendment to paragraph 0052 is believed to overcome the objection.

B. Rejections under 35 U.S.C. § 101

Claims 1 to 7 are rejected as being directed to non-statutory subject matter. More particularly, the Examiner asserts that the claims may be construed so broadly that they may encompass naturally occurring products. The present amendment clarifies that the claims are directed to an implantable composition that includes particular genetic coding sequences. Further, the amendment clarifies that expression of the sequences causes ablation of the AV node and thereby substantially extinguishes conduction through the node (see par. 0032 as basis for this amendment). Such a composition does not naturally occur, and represents the hand of the inventor (MPEP 2105). Consequently, the rejections under 35 U.S.C. § 101 should be withdrawn.

C. Rejections under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1 to 7 are rejected as not being clearly described in the specification. More particularly, the Examiner asserts that the claims as filed covered the genus of coding sequences that encode and express any molecule that suppresses cellular excitability, and that encode and express any protein that decreases conductance of an ion channel responsible for cellular excitability, while the specification only addresses three sequences that would fall under the

recited class. The Examiner then asserts that the written description of the invention does not sufficiently describe other members of the genus to represent that the inventor had, at the time of filing the application, possession of the entire genus.

In response to the rejection, claim 1 is amended to recite that the bio-ablation composition of the present invention includes a coding sequence that encodes and expresses a molecule that decreases expression of particular ion channels, namely, the L-type $Ca^{2+}$ channels as clearly disclosed in the present specification. The claim is also amended to recite that the composition further includes a coding sequence that encodes and expresses a protein that decreases the conductance of L-type $Ca^{2+}$ channels, which are clearly the primary targeted channels discussed in the present application with regard to a bio-ablation composition. In addition, newly added claims 51 to 56 further recite specific proteins corresponding to the claimed coding sequences. The claims as amended recite nucleic acid sequences that are of sufficient contemporary knowledge to clearly establish on their face and through reading the present specification that, at the time of filing the application, the inventors understood how to use the sequences to make and use the claimed compositions and proteins. Because the claims as amended recite specific sequences that are fully described in the specification as filed in terms of their origin and the proteins they encode, it is respectfully requested that the written description rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

D. Rejections under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1 to 7 are rejected as allegedly reciting subject matter that is not described in a manner whereby one who is skilled in the art would be enabled to make and use the invention. These rejections are respectfully traversed. It is respectfully submitted that when the proper test for enablement is applied to the amended and new claims, considered in light of the respective burdens upon the Patent Office and on an applicant for patent in establishing and responding to a

*prima facie* case of nonenablement, the claims should be found to be enabled and allowable.

i. Legal Test for Enablement:

The enablement requirement of § 112 ensures that one skilled in the art will be able to make and use a claimed invention. *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 599 (Fed. Cir. 1983). That some experimentation may be required does not preclude a finding of enablement so long as the amount of experimentation is not unduly extensive. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 316 (Fed. Cir. 1983). Furthermore, there is "no magical relation between the number of representative examples and the breath of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" *In re Borkowski*, 164 USPQ 642, 646 (CCPA 1970). A specification, in fact, need not contain a single working example. *Id*. 164 USPQ at 645.

The Office has the burden of establishing a lack of enablement. *In re Hogan*, 194 USPQ 527, 539 (CCPA 1977). Factors to be considered in determining whether pending claims would require undue experimentation have been articulated by the Federal Circuit in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). They include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The following discussion of the record in this case follows the illustrative approach to assessing enablement from the *Wands* opinion. Applicants include their comments and responses to the Office's analysis throughout the text that follows.

ii. Nature of the Invention and Breadth of the Claims

As recited in claim 1, the nature of the invention in a broad sense is a "bio-ablation composition comprising a first coding sequence that encodes and expresses, in atrioventricular node cells, a molecule that decreases expression of L-type $Ca^{2+}$ channels and thereby suppresses cellular excitability and a second coding sequence that encodes and expresses a protein that decreases the conductance of L-type $Ca^{2+}$ channels, wherein expression of both the first and second sequences is effective to substantially extinguish conduction through the atrioventricular node."

As set forth previously, the sequences recited in the independent claims, and the proteins they encode, are well understood in the art. Furthermore, in addition to the available literature describing such sequences and proteins, including those cited in the present specification and in the Action, the present specification clearly describes how to assemble and use the claimed compositions to produce the functional molecules. A person of skill in the art would recognize from reviewing the specification and the available literature cited therein how to make the claimed composition and proteins, and the functions that each encoded protein would perform in the cardiac atrioventricular node cells. Thus, the invention as recited in the pending claims is enabling in the sense that a person of skill in the art would be able to make and use the claimed composition and proteins.

iii. The State of the Prior Art and Its Predictability or Unpredictability

Four references are cited in the Action to illustrate what is considered to be the "state of the art" since or subsequent to July 2003 (when the parent patent application was filed) in the field of gene therapy. In Applicants' view, these references are not reflective of the full state of the art, or the nature of the present invention. Furthermore, even when viewed with high skepticism, the four cited references bolster the argument that the present specification is enabling. The Examiner cites what essentially amounts to prudent disclaimer language in

the references in an effort to assert that the art of cardiac gene therapy is in its infancy. Even though the references state that some obstacles or research existed before their disclosures may be implemented clinically in humans, this is well-recognized language to represent that further research is to be conducted, and to prevent criticism that the authors over-zealously promote the readiness of their discoveries for human use. Actually, when read as a whole, it is clear that the references disclose that protein molecules are produced to perform cardiac functions, the results are very promising. For example, Tomacelli et al. (Cardiovasc. Electrophysiol., May, 2003) identify several factors as obstacles toward routine human implementation of cardiac gene therapy. Yet, Tomacelli et al. proceed to cite numerous research articles that represent how each of the obstacles is being overcome (page 549, col. 2).

Also, it is well understood that for prudent and ethical researchers, human implementation of any drug or therapy is the last step in the testing process, and is only performed after successful results are obtained from in-vitro samples and/or from other animals. Of course, human testing has never been prerequisite for enablement when determining patentability of a drug or therapy.

Furthermore, the pending claims are not directed specifically to human therapy, but rather to bio-ablation compositions for a heart. Attached hereto are research articles that are more pertinent to the present invention than those cited by the Examiner. Beguin et al. (Nature, 2001) report that in transfected HEK293 cells, over-expressed kir/Gem inhibits expression of the L-type $Ca^{2+}$ channels, likely as a result of interaction between kir/Gem and the β-subunits of such channels. Murata et al. (Circ. Res., 2004) also reports that adenovirus-mediated delivery of kir/Gem markedly decreases L-type $Ca^{2+}$ channel current density in the atrioventricular node. Further, Donahue (Nature Medicine, 2004) and Bauer (Circ., 2004) report that overexpression of $G_i$ suppresses baseline atrioventricular conduction. Finally, the prior art cited by the Examiner in the subsequently-discussed rejections under 35 U.S.C. § 103(a) support enablement by

establishing successful genetic modification of cardiac cells using compositions expressing kir/Gen and $G_i$, which in turn shows predictablity in the related field.

iv. Amount of Direction or Guidance Presented and the Quantity of Experimentation

According to the Action, the three references cited therein and discussed above describe studies that reveal some technical obstacles. The Action also asserts that the application lacks sufficient guidance to surmount the technical difficulties recognized in the art. The Action's conclusion is that it would require undue experimentation for a skilled artisan to "make and use" the claimed invention as a bio-pacemaker. Essentially, the Examiner indicates that there is a lack of evidence in the present specification that a bio-pacemaker having any therapeutic utility may be manufactured without undue experimentation upon reviewing the present specification.

It is respectfully submitted that the Examiner is setting an inappropriately high bar for the amount of direction or guidance that the specification must provide. According to the Federal Circuit,

> "[t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. [citations omitted] The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed...." *In re Jackson*, 217 USPQ 804, 807 (Bd. App. 1982, cited with approval in *Wands*, 8 USPQ2d at 1404).

Even when "unpredictability" in a field such as gene therapy may create some doubt as to the accuracy of a broad statement supporting enablement, the Court of Customs and Patent Appeals (predecessor to the U.S. Court of Appeals for the Federal Circuit), has clearly articulated that

> "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with a contested statement." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1967).

Applicants contend that it would not require undue experimentation, given the specification and state-of-the-art as previously discussed, to make and use a bio-pacemaker by following the teachings of the present specification. As previously set forth, the cited references certainly do not anticipate or predict any failure for using at least two coding sequences, and the proteins they encode, together as a bio-ablation composition as set forth in the pending specification and claims. Without the cited references, the rejection in the Action is merely based on the Examiner's statements that the present specification is lacking in evidence to provide sufficient guidance. Yet, the specification is detailed and thorough in instructing how to assemble the claimed composition, and appropriate vehicles, construct, and associated promoters to enable expression of the encoded proteins in the atrioventricular node. In view of the foregoing remarks, and the amended and new claims, it is believed that the Office has not made out a *prima facie* case for nonenablement, and even if it has, this rejection is overcome by the amendments in view of the discussion above.

E. Rejections under 35 U.S.C. § 102(e)

Claims 1 to 2, and 6 to 7 are rejected as being anticipated by U.S. Publication US 2002/0155101 (Donahue). The rejections are respectfully traversed, at least in view of the present amendment. Claim 1 as amended recites a "bio-ablation composition comprising a first coding sequence that encodes and expresses, in atrioventricular node cells, a molecule that decreases expression of L-type $Ca^{2+}$ channels and thereby suppresses cellular excitability and a second coding sequence that encodes and expresses a protein that decreases the conductance of L-type $Ca^{2+}$ channels, wherein expression of both

the first and second sequences is effective to substantially extinguish conduction through the atrioventricular node."

In contrast, while Donahue discloses compositions that include sequences that encode $G\alpha_{i2}$, Donahue clearly fails to teach or suggest that the composition includes two sequences, one that expresses a molecule that decreases expression of L-type $Ca^{2+}$ channels, and one that expresses a protein that decreases the conductance of L-type $Ca^{2+}$ channels. Furthermore, while Donahue discloses that $G\alpha_{i2}$ has an inhibitory effect to a degree, Donahue clearly fails to disclose a composition that incorporates a plurality of sequences to provide a bio-ablation effect. For at least these reasons, the rejections under 35 U.S.C. § 102(e) should be withdrawn.

F. Rejections under 35 U.S.C. § 103(a)

Claims 1 to 5 are rejected as being unpatentable over Donahue in view of Circ. 106:19, 2002 (Murata). The rejections are respectfully traversed, at least in view of the present amendment. Although Donahue discloses compositions that include a sequence encoding $G\alpha_{i2}$, and Murata discloses compositions that include a sequence encoding kir/GEM, none of these references teaches or suggests using the sequences together for any purpose. The Examiner asserts that a person would be motivated to combine the sequences in a composition "in an experimental model." However, there is no evident goal behind such a combination. Furthermore, the present amendment establishes that the plurality of sequences are included in a composition for the purpose of bio-ablation, and such an effect is neither taught nor suggested by either Donahue nor Murata.

It is known that the rational to modify the prior art does not have to be expressly stated in the prior art, but may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law; however, Examiner must present a convincing line of reasoning supporting the rejection. There is no suggestion or motivation in the references that would render these elements obvious.

Therefore, Examiner's rejection must be based on knowledge generally available to one of ordinary skill in the art. However, Examiner has given no indication that these limitations are impliedly contained in the prior art or that it may be reasoned from knowledge generally available to the skilled practitioner or established by scientific principles or legal precedent. For at least these reasons, the rejections under 35 U.S.C. § 103(a) should be withdrawn.

There being no further outstanding objections or rejections, it is submitted that the application is in condition for allowance. An early action to that effect is courteously solicited.

Finally, if there are any formal matters remaining after this Amendment, the Examiner is requested to telephone the undersigned attorney to attend to those matters. The Commissioner is authorized to charge any deficiencies and credit any overpayments to Deposit Account No. 13-2546.

Respectfully submitted,

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Date

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